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CLINICAL PRACTICE

Dexmedetomidine pharmacokinetic–pharmacodynamic modelling in healthy volunteers: 1. Influence of arousal on bispectral index and sedation

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Abstract

Background. Dexmedetomidine, a selective α_2 -adrenoreceptor agonist, has unique characteristics, such as maintained respiratory drive and production of arousable sedation. We describe development of a pharmacokinetic–pharmacodynamic model of the sedative properties of dexmedetomidine, taking into account the effect of stimulation on its sedative properties.

Methods. In a two-period, randomized study in 18 healthy volunteers, dexmedetomidine was delivered in a step-up fashion by means of target-controlled infusion using the Dyck model. Volunteers were randomized to a session without background noise and a session with pre-recorded looped operating room background noise. Exploratory pharmacokinetic–pharmacodynamic modelling and covariate analysis were conducted in NONMEM using bispectral index (BIS) monitoring of processed EEG.

Results. We found that both stimulation at the time of Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale scoring and the presence or absence of ambient noise had an effect on the sedative properties of dexmedetomidine. The stimuli associated with MOAA/S scoring increased the BIS of sedated volunteers because of a transient 170% increase in the effect-site concentration necessary to reach half of the maximal effect. In contrast, volunteers deprived of ambient noise were more resistant to dexmedetomidine and required, on average, 32% higher effect-site concentrations for the same effect as subjects who were exposed to background operating room noise.

Conclusions. The new pharmacokinetic–pharmacodynamic models might be used for effect-site rather than plasma concentration target-controlled infusion for dexmedetomidine in clinical practice, thereby allowing tighter control over the desired level of sedation.

Clinical trial registration. NCT01879865.

Key words: dexmedetomidine; healthy volunteers; hypnotics and sedatives; noise; pharmacology

Editor's key points

- Most target-controlled infusion (TCI) programmes are based on plasma concentrations rather than effect-site concentrations.
- Using a previously developed pharmacokinetic model, effect-site concentrations were modelled from bispectral index and sedation scale pharmacodynamic data in 18 healthy volunteers.
- The resulting pharmacokinetic–pharmacodynamic model will be useful in developing improved TCI programmes that more tightly control sedation using effect-site concentrations.

Dexmedetomidine use in clinical practice is popular because of its unique characteristics as a selective α_2 -adrenoceptor agonist. It is currently licensed for sedation in intensive care units in Europe and the USA and for procedural sedation in the USA. Moreover, there is frequent off-label use, for instance for procedural sedation (in Europe), sedation during awake fiberoptic intubation, and awake craniotomies. Patients under dexmedetomidine sedation experience little respiratory depression, are more easily roused, and are better able to communicate compared with propofol or midazolam sedation.¹ Also, dexmedetomidine has been investigated as a possible opioid-reducing technique² and might attenuate perioperative inflammatory responses.³

For sedation in intensive care units, a slow titration to effect, with or without a loading dose, is acceptable, because a fast onset of effect is often not necessary. However, during procedural sedation or in the operating room, a faster onset of effect is often desired. Fast titration to the desired effect with limited or no overshoot, thereby limiting potential side-effects, can be attained using target-controlled infusion (TCI). For effect-site TCI, an accurate pharmacokinetic–pharmacodynamic (PKPD) model is necessary. Currently, only pharmacokinetic (PK) models are available for dexmedetomidine; no PKPD models.

We recently published an optimized dexmedetomidine PK model.⁴ In this twin paper, we describe the pharmacodynamic effects of dexmedetomidine in healthy volunteers, and model these effects into PKPD models. In this article, we describe and model the sedative effects of dexmedetomidine using our previously published PK model, and using bispectral index (BIS) and the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) as measures of sedative effects. In an accompanying paper,⁵ we describe and model the haemodynamic effects of dexmedetomidine.

Methods**Study design**

This study was approved by the local medical ethics review committee (METC, University Medical Center Groningen, Groningen, the Netherlands; METC number: 2012/400) and was registered in the ClinicalTrials.gov database (NCT01879865). Written informed consent was obtained from all volunteers. The study conduct was described in detail by Hannivoort and colleagues,⁴ who reported on the development of a pharmacokinetic model based on measured dexmedetomidine plasma concentrations collected throughout the study.

In brief, 18 healthy volunteers, nine male and nine female, stratified according to age and sex (18–34, 35–54, and 55–72 yr) received dexmedetomidine i.v. on two separate occasions, at

least 1 week and at most 3 weeks apart. Both sessions were identical in protocol, except for the use of acoustic noise-cancelling headphones (Bose QuietComfort 15, Framingham, MA, USA), either without background noise or with pre-recorded looped operating room background noise (monitor beeps and alarms, air conditioning noise, talking, equipment noise etc.). In both sessions, the volunteers were instructed to keep their eyes closed throughout the session, and they were stimulated as little as possible apart from at set times for the assessment of depth of sedation. Randomization using sealed envelopes was used to determine the order of the 'background silence' and 'background noise' sessions.

Standard anaesthesia monitoring was applied, with the inclusion of an arterial line for blood pressure monitoring and blood sampling, as described by Hannivoort and colleagues.⁴ An initial short infusion, given at $6 \mu\text{g kg}^{-1} \text{h}^{-1}$ for 20 s, was followed by a 10 min recovery period. Thereafter, dexmedetomidine was delivered as a TCI using the Dyck model⁶ with step-wise increasing targets of 1, 2, 3, 4, 6, and 8 ng ml^{-1} . Each target was maintained for 30 min. The maximal infusion rate was limited to $6 \mu\text{g kg}^{-1} \text{h}^{-1}$ for the first four steps; for the target of 6 and 8 ng ml^{-1} , the maximal infusion rate was increased to $10 \mu\text{g kg}^{-1} \text{h}^{-1}$ to facilitate attainment of the target within a reasonable time. Volunteers were monitored until 300 min after cessation of the TCI dexmedetomidine infusion. The syringe pump (Orchestra® Module DPS, Orchestra® Base A; Fresenius Kabi, Bad Homburg, Germany) that was used to deliver the dexmedetomidine infusion was controlled by RUGLOOP II software (Demed, Temse, Belgium) programmed with the Dyck model.⁶

Pharmacodynamic measurements

A BIS Vista monitor (Covidien, Boulder, CO, USA) was used to record BIS continuously to study depth of hypnosis. The MOAA/S scale was used to quantify the level of sedation and rousability of the volunteer at the following time points: immediately before the start of dexmedetomidine infusion, 2 min after the start of the initial short infusion, immediately before the start of the TCI infusion, and at the end of each TCI target step. During the recovery period, MOAA/S scores were recorded every 2 min for the first 30 min, and every 10 min thereafter, until the volunteer reached the maximal score on the MOAA/S scale. All monitored parameters were recorded electronically using RUGLOOP II software.

Data handling

The final data set contained BIS measurements at a sampling rate of 1 Hz, which, for some subjects, resulted in >30 000 observations per session. To reduce the computational burden, we reduced the number of BIS measurements per subject. We also applied a median filter to reduce the influence of artifacts, outlying data, or both during model development. The width (span) of the median filter was 60 s. Data reduction was performed by retaining the first out of every 50 consecutive median filtered observations.

The data set used for modelling contained a median of 372 (range 115–556) BIS measurements per subject per session, corresponding to a sampling rate of $\sim 1 \text{ min}^{-1}$. All unfiltered MOAA/S observations were retained in the data set, with a median of 25 (range 8–40) observations per subject per session.

Population pharmacokinetic–pharmacodynamic modelling

The PKPD modelling was based on individual PK parameter estimates from the dexmedetomidine PK model published

previously.⁴ The individual predicted PK parameters (V_1 , V_2 , V_3 , CL , Q_2 , and Q_3) derived from this model were fixed for each individual and each session (Hannivoort and colleagues⁴ reported that V_1 was different between occasions) during further pharmacodynamic (PD) modelling.

Different structural models were evaluated to test whether hysteresis exists between the individually predicted dexmedetomidine plasma concentrations (IPRED_{plasma}) and PD measures. Direct models relating IPRED_{plasma} directly to the PD measure were compared against delay drug effect models, such as an effect compartment model or an indirect response model. Drug effects were described using linear, E_{\max} and sigmoid E_{\max} models.

Once the base model structure was established, graphical analysis was conducted to identify potential correlations between *post hoc* predicted PKPD parameters and subject covariates. Subject covariates considered were as follows: weight, height, BMI, age, sex, and session (background silence vs background noise). These covariates were tested in the model, and the resulting change in goodness of fit (GOF) was evaluated. For the continuous covariates (age, height, and weight), a linear relationship was assumed, whereas for the categorical covariate (sex), an additional parameter was added to differentiate between males and females. Where appropriate, inclusion of model parameters, covariates, or both was tested at the 5% significance level by comparing the decrease in objective function (OFV) against the critical quantile of the corresponding χ^2 distribution (e.g. a 3.84 decrease in OFV for inclusion or exclusion of a single parameter).

Population pharmacodynamic modelling of the confounding effect of the rousability on BIS

During dexmedetomidine sedation, the stimulation inherent in MOAA/S scoring results in a transient increase (arousal) in BIS. The MOAA/S observations were regarded as a sudden, instantaneous stimulation of the subject, and the perturbation in BIS was modelled as a leftward shift in the effect-site concentration necessary to reach half of the maximal effect (C_{50}). Thus, there are two BIS curves corresponding to a stimulated (aroused) and unstimulated (non-aroused) pharmacodynamic state. The dissipation of arousal (equation 1) was modelled using a single parameter (k_{in}), in conjunction with an indirect response model (IRM). The pharmacodynamic arousal state is used as a linear interpolation between two sigmoid drug effect models (given by equations 2 and 3), as described in equation (4):

$$\frac{dRELAX}{dt} = k_{in} \times [(1 - A(RELAX))] \quad (1)$$

$$BIS_{i,NSTIM} = \text{Baseline BIS}_i \times \left(1 - \frac{C_e}{C_e + C_{50,i}}\right) \quad (2)$$

$$BIS_{i,STIM} = \text{Baseline BIS}_i \times \left(1 - \frac{C_e}{C_e + [C_{50,i} \times (1 + \Delta C_{50,i})]}\right) \quad (3)$$

$$BIS_i(t) = BIS_{i,NSTIM} \times A(RELAX) + BIS_{i,STIM} \times (1 - A(RELAX)) \quad (4)$$

In short, an unstimulated subject is in a state of relaxation (i.e. non-aroused), during which the 'amount' in the relaxation compartment [i.e. $A(RELAX)$] equals 1. At the moment of stimulation, the compartment is reset, i.e. the 'amount' in this compartment is set to zero, corresponding to a stimulated, aroused state. Thereafter, the state returns to a state of relaxation at a rate of k_{in} . As seen from equation (4), the amount in the

relaxation compartment is used as a linear interpolation between an unstimulated (equation 2) and a stimulated (equation 3) BIS model. In equations (2) and (3), the dexmedetomidine effect-site concentration (C_e) to achieve half of the maximal decrease in BIS in an unstimulated patient is given by C_{50} , whereas the proportional change in the C_{50} for a stimulated subject is described by ΔC_{50} .

Population pharmacodynamic modelling of categorical MOAA/S observations

Categorical MOAA/S observations were modelled using a model for ordered categorical variables. This model was parameterized such that the parameters estimate cumulative probabilities (e.g. the probability of observing an MOAA/S score ≤ 3) on the logit scale. Inter-individual variability (IIV) and drug effect were implemented on these baseline logits using an exponential and an additive component, respectively. Inclusion of random effects beyond the IIV on the baseline logits was not considered to avoid issues with identifiability of the model parameters. Equation (5) gives an example of the model for the logit of the cumulative probability (Pr) of observing an MOAA/S score ≤ 3 .

$$\text{Logit}(\text{Pr}[\text{MOAA/S} \leq 3]) = \theta_{LLE0} \times e^{\eta_i} + \theta_{\Delta 01} + \theta_{\Delta 12} + \theta_{\Delta 23} + \frac{E_{\max} \times C_e^\gamma}{C_{50}^\gamma + C_e^\gamma} \quad (5)$$

The baseline logit is described by a typical value for the logit to be equal to zero (θ_{LLE0}), including an exponential random effect (η_i) on this logit and additional terms to estimate the difference between successive logits (e.g. $\theta_{\Delta 01}$ estimates the difference between the logit for an MOAA/S score ≤ 1 and the logit of MOAA/S=0). The drug acts to increase the baseline logit according to a sigmoid E_{\max} model based on the predicted effect-site concentration (C_e). The parameters of this sigmoid E_{\max} model describe the maximal change in the logit (E_{\max}), the effect-site concentration necessary to reach half of the maximal effect (C_{50}) and the Hill coefficient of the concentration–effect relationship (γ). The logits were back-transformed to cumulative probabilities using the inverse of the logit transformation. Subsequently, the probabilities for each category were obtained by subtraction from the cumulative probabilities, with the probability to observe an MOAA/S score ≤ 5 being 1.

Parameter estimation and model evaluation

The first-order conditional estimation algorithm with interaction (FOCE-I) as implemented in NONMEM[®] (version 7.3; Icon Development Solutions, Hannover, MD, USA) was used to fit BIS data. For the categorical MOAA/S data, the Laplacian approximation to the likelihood was used. Inter-individual variability and inter-occasion variability (IOV) were modelled using an exponential model. Residual unexplained variability was described using additive or proportional error models, or both.

During model building, the GOF of the different models was compared numerically using the Akaike information criterion (AIC) and the median absolute (population-) prediction error (MdAPE). At each stage, GOF was graphically evaluated by inspecting plots of the individual or population predicted vs observed responses, and plots of the conditionally weighted residuals (CWRES) vs individual predictions and time. As a safeguard to over-parameterization, only models with a condition

number of the Fisher information matrix (FIM) <500 were retained in the model building hierarchy. Finally, models were validated internally using prediction-corrected visual predictive checks (pcVPC) according to Bergstrand and colleagues.⁷

All models were fitted to the data using PsN⁸ and Pirana⁹ as back or front end, or both, to NONMEM[®]. The numerical and graphical assessment of the GOF and the construction of the pcVPCs were conducted in R[®] (R Foundation for Statistical Computing, Vienna, Austria). All simulations were performed in a Microsoft Excel Macro-Enabled Worksheet (Microsoft Office Professional Plus 2013), which is supplied in the Online Supplementary material. The worksheet depends on the 'PKPD tools for Excel' package developed by T. Schnider and C. Minto, which is available from <http://www.pkpdtools.com/excel> (last accessed April 18th 2017).

Statistical analysis

All model parameters are reported as typical values with associated relative standard errors (RSE) and 95% confidence intervals (CIs) derived from log-likelihood profiling.¹⁰

Results

Data

Figure 1 shows the median filtered BIS signal and the observed MOAA/S for four representative subjects from our study during the step-up TCI administration. The dashed lines indicate when a new TCI target was set. Immediately before changing the TCI

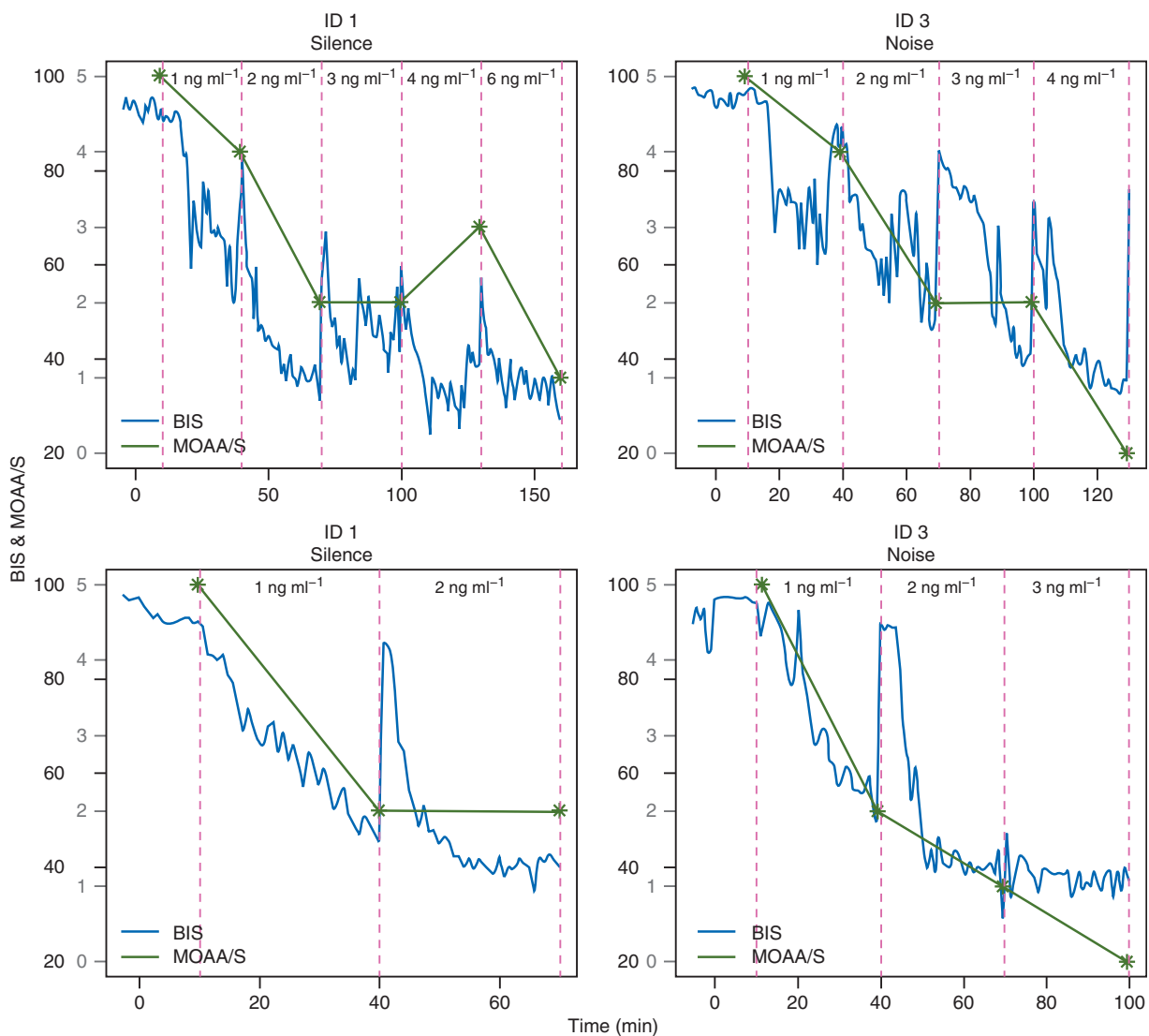


Fig 1 Median filtered BIS values and MOAA/S observations for the step-up TCI administration for four representative subjects. Dashed vertical lines indicate when a new TCI target was set. Immediately before this, MOAA/S was assessed. BIS, bispectral index; MOAA/S, Modified Observer's Assessment of Alertness/Sedation; TCI, target-controlled infusion.

target, MOAA/S was scored. This figure clearly shows the perturbation in the BIS signal induced by stimulating the subjects at the time of MOAA/S scoring and the subsequent attenuation of the effect of stimulation. The complete time courses of BIS and MOAA/S observations for all subjects used for modelling are shown in Online Supplementary Figs S1 and S2.

Model development for BIS

In a first attempt to describe the effect of dexmedetomidine on BIS measurements, a sigmoid E_{\max} model was used. Rousability was accounted for according to equations (1)–(4), and the delay between plasma PK and BIS effects was described using an effect compartment model. Modifications to this base structure were evaluated. Firstly, the Hill coefficient (γ) was fixed to 1, resulting in a decrease in the condition number from 1327 to 120; at the same time, the MdAPE decreased from 13.1 to 13.0%. Secondly, a logit transform, as shown in equations (6) and (7), was used to describe the intersubject variability in BIS at baseline. The inclusion of the logit transformation decreased the MdAPE further to 12.8%. Under this transformation, all baseline BIS predictions are restricted between 0 and 100. This significantly improved the pcVPC for the BIS model.

$$\text{Baseline BIS}_i = 100 \times \left(\frac{e^{\text{Logit}_i}}{1 + e^{\text{Logit}_i}} \right) \quad (6)$$

$$\text{Logit}_i = \log \left(\frac{\left(\frac{\text{Baseline BIS}}{100} \right)}{1 - \left(\frac{\text{Baseline BIS}}{100} \right)} \right) + \eta_i \quad (7)$$

The significance of the rousability component of the model was evaluated by exclusion of this component, as described by equations (1), (2) and (4), from the final model. The resulting decrease in GOF ($\Delta\text{AIC}=+2358$) and simultaneous increase in the MdAPE to 13.5% underpin the importance of accounting for arousal in the BIS model. Furthermore, a comparison between the parameter estimates for both models revealed a significant shift in k_{e0} (0.120 vs 0.991 min^{-1}), baseline BIS (96.8 vs 89.7), and C_{50} (2.63 vs 4.78 ng ml^{-1}) upon removal of the rousability component. Inclusion of inter-occasion variability on the estimated PKPD parameters did not significantly improve the GOF of the model. Inclusion of age, weight, height, or sex did not result in a significant decrease in the OFV. Therefore, no covariates were included in the final model.

Final model for BIS

The final model parameters are described in Table 1. The likelihood profiles, which were generated to identify potential problems with parameter identification, are shown in Online Supplementary Fig. S3. Goodness-of-fit plots, such as *post hoc* predictions vs observations and CWRES vs time, are shown in Fig. 2. Online Supplementary Fig. S4 shows the pcVPC. Overall, these figures demonstrate that the presented model adequately describes observed changes in BIS during and after dexmedetomidine administration and that all parameters of the model are estimated with acceptable precision.

We found that changes in plasma dexmedetomidine concentrations are reflected in BIS, with a half-life of effect-site equilibration of 5.8 min. In unstimulated subjects, half of the maximal effect ($\sim\text{BIS}_{48}$) is attained at 2.63 ng ml^{-1} . In the stimulated state, patients achieve a BIS value of 48, on average, when the dexmedetomidine effect-site concentration approaches 7.13 ng ml^{-1} . The *post hoc* predicted values of C_{50} and ΔC_{50} were found to be

Table 1 Final model parameters with associated relative standard errors (expressed as percentages) derived from log-likelihood profiling. *Calculated according to: $\sqrt{e^{\omega} - 1} \times 100\%$. ω , estimated variance of the inter-individual variability (IIV). †Derived from log-likelihood profiling. ‡Expressed as SD. §Expressed as SD in the logit domain. §Dimensionless parameter. For the volunteer cohort exposed to ambient operating room noise, the C_{50} is given by $C_{50} \times (1 - \Delta C_{50, \text{noise cohort}})$

		Final BIS model	
Parameter		Estimate (RSE% [†])	IIV* (RSE% [†])
θ_1	$\text{Base}_{\text{BIS}}^{\S}$	96.8 (1.20)	1.34 [†] (56.3)
θ_2	$k_{e0\text{BIS}}$ (min^{-1})	0.120 (3.80)	—
θ_3	C_{50} (ng ml^{-1})	2.63 (15.9)	69.5 (40.2)
θ_4	ΔC_{50}^{\S}	1.71 (18.3)	81.8 (40.8)
θ_5	k_{in} (min^{-1})	0.130 (24.6)	122 (41.1)
	$\sigma_{\text{RUV, Additive}}^{\ddagger}$	10.6 (1.20)	—
		Final MOAA/S model	
Parameter		Estimate (RSE% [†])	IIV* (RSE% [†])
θ_6	$\theta_{\text{LLE0}}^{\S}$	−10.1 (14.6)	12.5 (37.4)
θ_7	$\theta_{\Delta 01}^{\S}$	0.394 (14.0)	—
θ_8	$\theta_{\Delta 12}^{\S}$	1.83 (5.6)	—
θ_9	$\theta_{\Delta 23}^{\S}$	1.13 (7.7)	—
θ_{10}	$\theta_{\Delta 34}^{\S}$	1.55 (9.1)	—
θ_{11}	$k_{e0\text{MOAA/S}}$ (min^{-1})	0.0428 (17.0)	—
θ_{12}	C_{50} (ng ml^{-1})	0.428 (25.6)	—
θ_{13}	E_{\max}^{\S}	10.4 (13.3)	—
θ_{14}	$\Delta C_{50, \text{noise cohort}}^{\S}$	0.316 (35.0)	—

uncorrelated but highly variable within our study population. Inter-individual variability was estimated to be 69.5 and 81.8% for C_{50} and ΔC_{50} , respectively. The model illustrates that the effect of stimulation attenuates slowly, with an estimated half-life of 5.3 min. Moreover, the time for the BIS signal to normalize is highly variable within our study population, with 95% of the estimates for the half-life of attenuation between 0.82 and 34.6 min.

Model development for MOAA/S

As a starting point, a linear drug effect model was used to describe dexmedetomidine-induced changes in the logit of the cumulative probabilities. Subsequently, the model was refined by introducing the following: (i) an E_{\max} drug effect model ($\Delta\text{AIC}=-173.3$); and (ii) inter-individual variability on the baseline logit of observing an MOAA/S score equal to 0 (θ_{LLE0} ; $\Delta\text{AIC}=-187.6$). The assumption of proportional odds was challenged by fitting a differential odds model, as described by Kjellsson and colleagues.¹¹ The differential odds model had a slightly lower AIC ($\Delta\text{AIC}=-6.7$) compared with our final model. However, the condition number of the Fisher information matrix (FIM) was high (1110), and no differences were seen between the pcVPCs of both models. Based on these findings, we decided not to implement the differential odds assumption into our final model.

In line with our approach to model the influence of the rousability on the BIS signal, we evaluated a model with an additional E_{\max} curve to model potential transient changes in MOAA/S scores attributable to subject stimulation inherent in

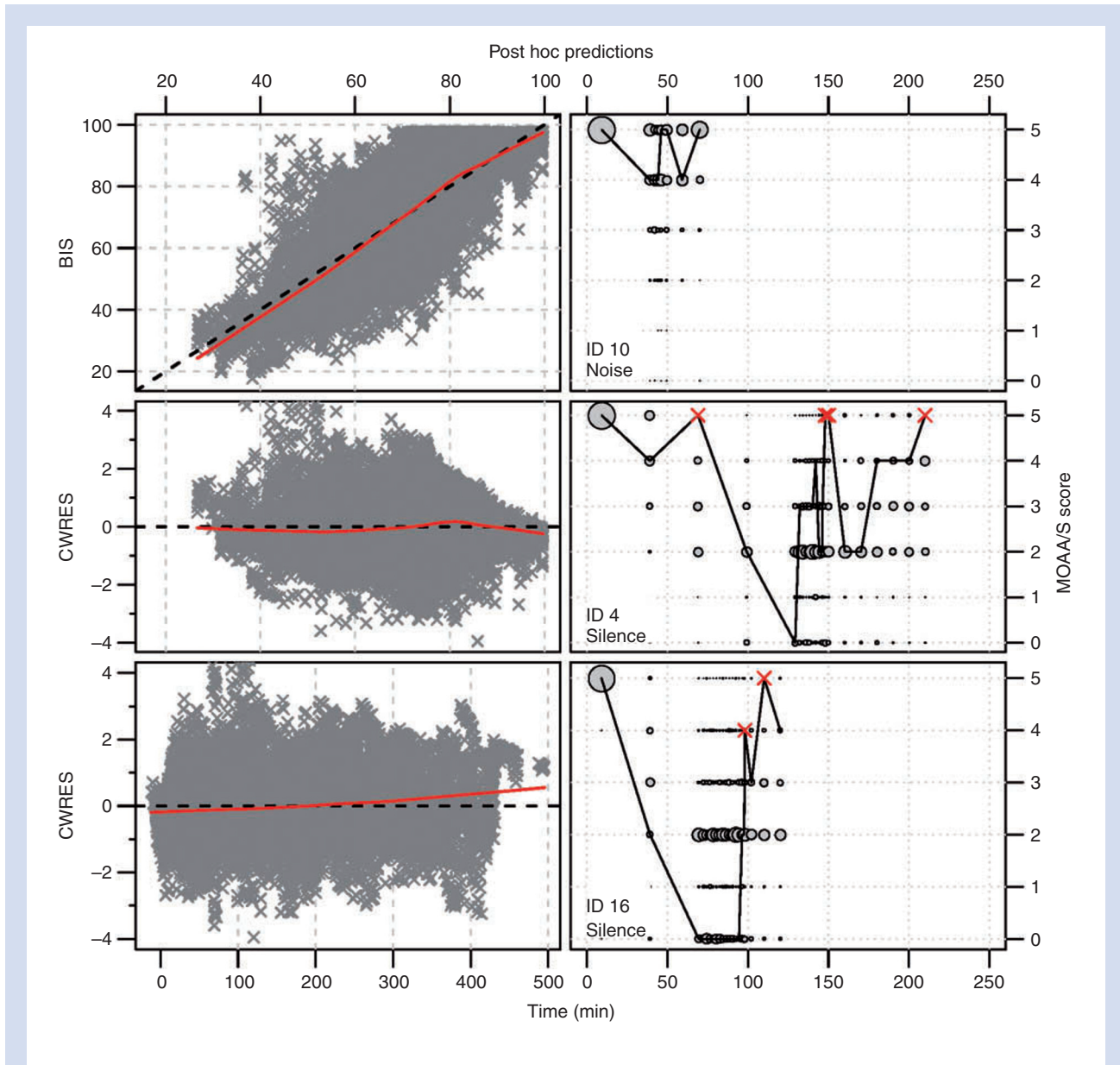


Fig 2 Goodness-of-fit plots for the final model. The left panels show the observed BIS vs the post hoc predictions and the CWRES against post hoc predictions and time. The continuous red line depicts a non-parametric smoother through the data to illustrate lack of bias in the different plots. The right panels show individual GOF plots for the three subjects with the best, median, and worst fit, respectively. The continuous black line shows the observed MOAA/S scores, whereas grey circles denote the probability of observing the MOAA/S scores, with bigger circles having higher probabilities. These probabilities were estimated by simulation using the post hoc predicted parameters. Red crosses indicate regions where, according to the simulations, the probability for the observed MOAA/S is <10%. These points served as 'residuals' to instruct on how to refine the model. BIS, bispectral index; CWRES, conditionally weighted residuals; GOF, goodness of fit; MOAA/S, Modified Observer's Assessment of Alertness/Sedation.

MOAA/S scoring. This modification led to a marginal improvement in GOF ($\Delta\text{AIC} = -13.9$ for two additional parameters). The estimate for the half-life of attenuation was significantly lower than what was found for the BIS model (0.65 vs 5.3 min, respectively), whereas the estimate for the ΔC_{50} was significantly larger (4.21 vs 1.71). The predictive performance, as evaluated by pcVPC, did not improve, and the model suffered from some numerical difficulties, resulting in a high condition number (1203). Overall, these findings led us to the decision not to include a

rousability component, describing the time-varying effect of rousability on the MOAA/S, in our final model.

Covariate screening identified session (background silence vs background noise session) as a significant covariate. Inclusion of session as a covariate on the C_{50} led to a significant increase in GOF ($\Delta\text{AIC} = -10.5$). The effect of the covariate was confirmed by graphical analysis of the raw data stratified by session. This graphical analysis confirmed that the distribution of MOAA/S scores as a function of TCI targets was different

between both sessions (data not shown). Inclusion of the covariate did not increase the condition number of the FIM and was therefore retained in the final model. Age, weight, height, and sex were found not to have a significant impact on the OFV. Furthermore, introduction of inter-occasion variability also did not improve the GOF of the model.

Final model for MOAA/S

The final model parameters and associated standard errors are shown in Table 1. Online Supplementary Fig. S3 shows the likelihood profiles for the final model. The GOF of the final model, for three subjects representing the best, median, and worst fit, respectively, is shown in Fig. 2 (*post hoc* predicted vs observed MOAA/S scores as a function of time for all subjects are shown in Online Supplementary Fig. S2). Simulation-based GOF diagnostic plots are favoured here owing to the inability to calculate individually predicted dexmedetomidine plasma concentrations and conditionally weighted residuals-based diagnostic plots for ordered categorical models. A visual predictive check for the final model is shown in Online Supplementary Fig. S5. Overall, these diagnostics show that our final model is adequately developed and that the predictive performance is sufficient to characterize our observations.

The equilibration between effect-site concentrations and plasma concentrations for dexmedetomidine is fairly slow, with an estimated half-life for effect-site equilibration of 14 min. Subjects who were deprived of normal ambient background noise from the operating room achieved half of the maximal MOAA/S effect at an effect-site concentration of 0.43 ng ml^{-1} . Volunteers who were exposed to background noises were somewhat more sensitive to the sedative effects of dexmedetomidine and achieved half of the maximal effect at an effect-site concentration that was, on average, 32% lower (i.e. 0.29 ng ml^{-1}).

According to the model, the difference between the logit of observing an MOAA/S of 0 and an MOAA/S score ≤ 1 is small ($\Delta_{01}=0.394$). Compared with the other estimates for the differences in logits, this small estimate results in a fairly low predicted probability of observing an MOAA/S 1. This is in line with our observations. Indeed, when we look at the observed proportion of MOAA/S 1 across time (black line in Online Supplementary Fig. S5) we see that, as opposed to the other MOAA/S categories, the profile for observing an MOAA/S 1 is relatively flat, not exceeding 10%. An overview of the probability of observing the different MOAA/S scores as a function of effect-site concentration is given in Fig. 3 and commented on further in the Discussion.

Discussion

We developed a PKPD model that characterizes the relationship between dexmedetomidine plasma concentrations and the resulting changes in BIS and MOAA/S. Owing to the specific characteristics of dexmedetomidine, our models were built taking into account the time-varying rousability that was introduced by stimulation of the subject during MOAA/S scoring. Furthermore, our study protocol was such that we were able to determine the confounding effect of another type of stimulation, continuous background auditory stimulation, on the sedative properties of dexmedetomidine. A unique characteristic of our model is that it incorporates the rousability effect on BIS. Stimulation of subjects at the time of MOAA/S scoring induced a transient increase in the BIS signal. The effect of the stimulus diminishes over time and typically disappears within ~ 21 min

($4 \times t_{1/2}$) in the absence of stimulation. However, if the subject is stimulated more frequently, accumulation occurs and the 'stimulated' state persists for prolonged periods of time.

Our model also explains the potential for an apparent paradoxical response of transiently increasing hypnosis (decreasing BIS) in the presence of decreasing drug concentrations as the individual transitions from a stimulated to an unstimulated pharmacodynamic state. This is visible in Fig. 4, where the observed BIS signals during step-up TCI administration and the subsequent recovery for three subjects representing examples of the best, median, and worst fit of our model against the observed data are shown. The good agreement between the observed BIS signal and the *post hoc* predicted BIS curves (shown in blue) after single and repeated stimulation inspires confidence in the validity of our proposed PKPD model.

The basis for our MOAA/S model is an E_{\max} model, using the logit of cumulative probabilities of MOAA/S scores rather than the MOAA/S scores themselves. A time-varying rousability effect similar to the effect found for BIS was not retained in our final PKPD model describing MOAA/S observations. When we tried to estimate the half-life of attenuation, we found an estimate for k_{in} of 1.1 min^{-1} , corresponding to a $T_{1/2}$ of 0.65 min, indicating that, for the typical patient, the effect of stimulation disappears within 2.6 min. In the context of our protocol, in which MOAA/S were scored at least 2 min apart, inclusion of the time-varying rousability had no significant impact on the predicted probabilities. However, in other situations, where stimulation occurs more frequently, this might be important, and our suggested approach could be used to take the confounding effect of stimulation into account.

Our analysis showed that the C_{50} for MOAA/S was significantly higher, and thus subjects were more responsive, when deprived of ambient noise in comparison to exposure to ambient operating room noise. This could be because auditory impulses, such as the name of the volunteer being spoken, are more clearly perceived against a silent background. However, our model indicates that even responsiveness towards a painful stimulus was significantly different between sessions. This finding was confirmed by graphical analysis (data not shown) that showed that, after controlling for the TCI target, the frequency of MOAA/S 0 was significantly different between sessions. These results suggest that other more complex physiological phenomena might govern the interaction between the presence of background noise and the sedative properties of dexmedetomidine.

Surprisingly, we found no influence of age on sensitivity to the sedative effects of dexmedetomidine. Inclusion of age as a covariate on θ_{LLE0} and C_{50} in the MOAA/S and BIS model did not result in a significant decrease in the OFV. In contrast to this finding, Schnider and colleagues¹² and Minto and colleagues¹³ found that for propofol and remifentanyl the sensitivity to EEG effects increases with age. By including volunteers into our study in age- and sex-stratified cohorts, we maximized the *a priori* possibility of detecting a potential influence of age and sex on the sedative properties of dexmedetomidine. Nevertheless, the limited number of subjects in our study could have obscured an age effect. In contrast, the different receptor pathways involved in dexmedetomidine sedation (α_2 -receptor agonist) vs propofol (GABA_A receptor agonist) and remifentanyl (opioid) sedation might explain the lack of an age effect.

Our PKPD models allow us to define target effect-site concentrations that maximize the possibility of attaining a particular level of sedation and inform us on the BIS values that correspond to these sedation levels. In a subject exposed to

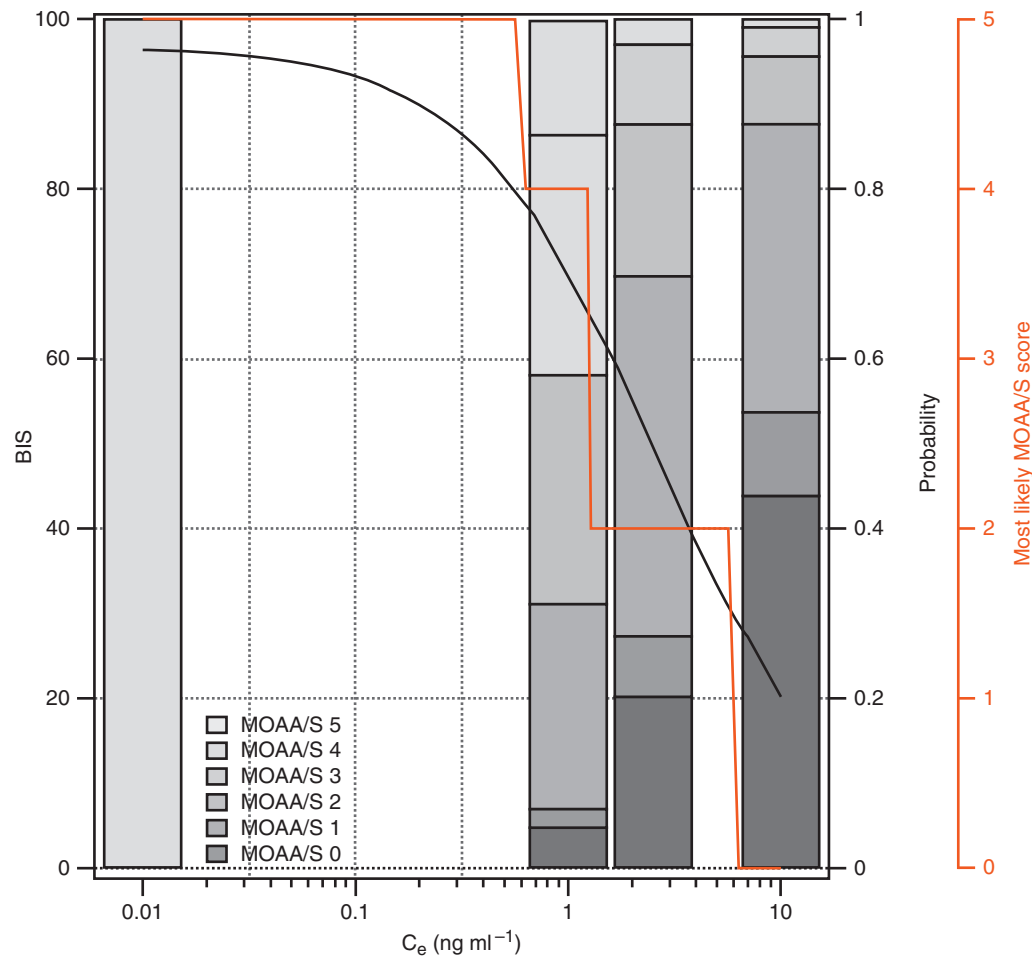


Fig 3 Relationship between effect-site concentrations and BIS and MOAA/S. The continuous black line is the predicted BIS, whereas the MOAA/S with the highest probability is shown with a continuous red line. Stacked bar plots illustrate the distribution of MOAA/S probabilities at effect-site concentrations of 0.01, 1.0, 2.5, and 10 ng ml^{-1} , corresponding to predicted BIS values of 96, 70, 50, and 20, respectively. C_e , effect-site concentration; BIS, bispectral index; MOAA/S, Modified Observer's Assessment of Alertness/Sedation.

ambient operating room noise, loss of responsiveness to verbal stimulation (i.e. MOAA/S score ≤ 2) is predicted to occur at an effect-site concentration of 0.91 ng ml^{-1} . At this effect-site concentration, BIS immediately before the MOAA/S stimulation is 72. Volunteers deprived of ambient noise lose responsiveness to verbal stimulation at a C_e of 1.3 ng ml^{-1} and BIS value of 64.

Based on a study in healthy volunteers, Kasuya and colleagues¹⁴ found that the correlation between BIS and MOAA/S scales is significantly different between dexmedetomidine and propofol. When considering the same level of sedation, BIS values for dexmedetomidine were generally lower than those in the propofol group. Our analysis contradicts these findings. The results in Table 2 are in (very) good agreement with earlier work on propofol. Struys and colleagues¹⁵ found that for propofol the BIS values where 50% of the population loses responsiveness (BIS_{50}) to MOAA/S scales 5, 4, and 3 were 85, 74, and 66, respectively. However, earlier findings by Kearse and colleagues¹⁶ and

Iselin-Chaves and colleagues¹⁷ showed that the BIS_{50} for loss of responsiveness to verbal stimulation was 65 and 64, respectively. These results are in good agreement with our estimates for dexmedetomidine, indicating that the calibration for BIS is very similar between dexmedetomidine and propofol. Overall, these findings suggest that target BIS values between 60 and 40, which generally indicate adequate general anaesthesia, are appropriate when dexmedetomidine-based deep sedation is required. Between these target BIS values, corresponding to a C_e of 1.6 and 3.6 ng ml^{-1} , loss of responsiveness to verbal stimulation is predicted to occur in 58 and 81% of patients, respectively, and MOAA/S scores will be ≤ 2 .

Besides the discrepancy with the work of Kasuya and colleagues,¹⁴ our results are generally in line with earlier reports from experimental studies with dexmedetomidine in healthy volunteers. In a study where healthy volunteers received dexmedetomidine in a step-up TCI titration, Kaskinoro and colleagues¹⁸ found that, on average, loss of responsiveness to

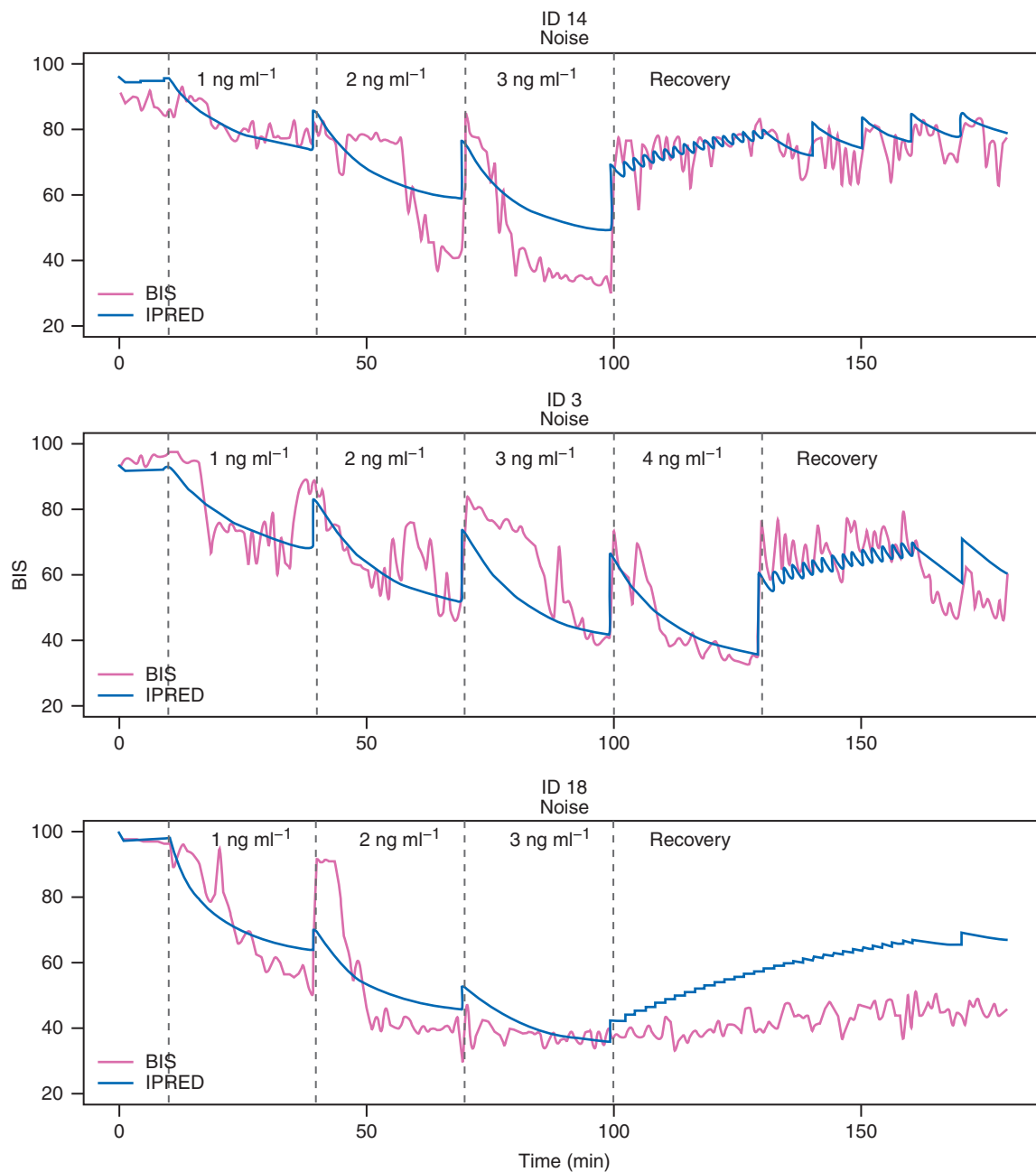


Fig 4 Observed (pink lines) and *post hoc* predicted BIS (blue lines) for the subjects with the best, median, and worst fit. The dashed vertical lines indicate when a new TCI target was set. Immediately before this, MOAA/S was assessed. BIS, bispectral index; MOAA/S, Modified Observer's Assessment of Alertness/Sedation; TCI, target-controlled infusion.

verbal stimulation occurred at 1.9 ng ml^{-1} . Although it is not entirely clear whether volunteers were exposed to or deprived of ambient noise, this concentration is in agreement with our predictions, considering the variability associated with assessment of loss of responsiveness to verbal stimulation. In a study where healthy volunteers received a $10 \text{ min } 6 \mu\text{g kg}^{-1} \text{ h}^{-1}$ loading dose followed by a 0.2 or $0.6 \mu\text{g kg}^{-1} \text{ h}^{-1}$ i.v. infusion, Hall and

colleagues¹⁹ found that BIS decreased by 31 and 36% after 60 min. When we simulated a similar experimental study, we found a 21 and 28% decrease in BIS, which is slightly lower, but still inspires confidence given that we are dealing with an independent data set and that it is not clear whether volunteers in the study by Hall and colleagues¹⁹ were stimulated, which could explain the higher BIS values.

Table 2 BIS₅₀ values and corresponding C_e dexmedetomidine for five levels of the MOAA/S score for subjects exposed to and deprived from ambient operating room noise

	Ambient operating room noise cohort		Silent cohort	
	C _e (ng ml ⁻¹)	BIS ₅₀	C _e (ng ml ⁻¹)	BIS ₅₀
Loss of MOAA/S 5	0.29	87	0.43	83
Loss of MOAA/S 4	0.54	80	0.79	74
Loss of MOAA/S 3	0.91	72	1.34	64
Loss of MOAA/S 2	4.10	38	5.99	29
Loss of MOAA/S 1	9.88	20	14.4	15

The approach we present, which models the drug effect in both the unstimulated and the stimulated state, was used previously by Heyse and colleagues²⁰ to account for the differences in hypnotic and analgesic effects between stimulated and unstimulated volunteers receiving sevoflurane–remifentanyl anaesthesia. However, in contrast to the analysis of Heyse and colleagues,²⁰ we used this approach to account for the time-varying effect of stimulation. Correcting for the confounding effect of stimulation is pivotal for modelling dexmedetomidine. Not only does it significantly increase the GOF, without the rousability component in the model a significant bias is seen in estimated PKPD parameters. For example, the C₅₀ for BIS, which is the parameter of primary interest, increases by 82% after stimulation. Dosing regimens taking into account both the pre- and post-stimulation effects with dexmedetomidine could result in better titration, targeting values with the highest probability for the desired MOAA/S. If deep sedation is required, the target that results in the least increase in BIS without oversedating the patient could be chosen. Whenever BIS is used to target a specific degree of sedation with dexmedetomidine, one should be aware of the confounding effect of stimulation. An applied stimulus is expected to disturb the BIS signal for up to 20 min. Implementing our model into a drug display could correct for this time-varying effect of stimulation and could provide a more robust system to titrate dexmedetomidine-based sedation.

In conclusion, we present a PKPD model that adequately describes the sedative and hypnotic effects of dexmedetomidine in healthy volunteers. This model integrates the well-known rousability associated with dexmedetomidine sedation and accounts for changes in responsiveness between volunteers attributable to repeated auditory stimulation. After validation of our PKPD model in a patient population, our model might be used to transition towards effect-site TCI rather than plasma concentration TCI for dexmedetomidine in clinical practice, thereby allowing tighter control over the desired level of sedation.

Authors' contributions

Study design: L.N.H., H.E.M.V., A.R.A., M.M.R.F.S.
 Patient recruitment: L.N.H., H.E.M.V., K.M.E.M.R.
 Data collection: L.N.H., H.E.M.V., K.M.E.M.R.
 Data analysis: P.C., D.J.E., A.R.A., M.M.R.F.S.
 First draft of the paper: P.C.
 Revision of the manuscript: L.N.H., H.E.M.V., D.J.E., K.M.E.M.R., A.R.A., M.M.R.F.S.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Declaration of interest

P.C., L.N.H., D.J.E., H.E.M.V.: none declared.

K.M.E.M.R.: member of the KOL group on patient warming and received funding for travel and lectures of the 37°company (Amersfoort, The Netherlands).

A.R.A.: his research group/department received grants and funding from The Medicines Company (Parsippany, NJ, USA), Dräger (Lubeck, Germany), Carefusion (San Diego, CA, USA), Orion, and B Braun (Melsungen, Germany). He is a paid consultant to Janssen Pharma (Belgium), Carefusion (San Diego, CA, USA), and The Medicines Company (Parsippany, NJ, USA). He is an editor of the *British Journal of Anaesthesia*.

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